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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/822,186	03/20/97	RUEGER	D CRP-137

HM12/0817

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EXAMINER	
ROMEO,D	
ART UNIT	**PAPER NUMBER**
1646	21

DATE MAILED: 08/17/99

Please find below and/or attached an Office communication concerning this appiication or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/822,186	Rueger et al.
Examiner	**Group Art Unit**
David S. Romeo	1646

☒ Responsive to communication(s) filed on *5-27-99*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-25, 32, 33, 35, and 36* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-25, 32, 33, 35, and 36* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-25, 32, 33, 35, and 36* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *14*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

[redacted]

DETAILED ACTION

1. The amendment filed 05/27/99 (Paper No. 20) has been entered in full.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Applicant's election without traverse of group I, claims 1-25, 31-33, 35 and 36 in Paper No. 20 is acknowledged.

4. Claims 26-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 20.

5. Applicant's election without traverse of OP-1, carboxymethyl cellulose, collagen, critical size defects in Paper No. 20 is acknowledged.

6. Claims 1-25, 31-33, 35 and 36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) to the extent that they are drawn to a non-elected species. Election was made **without** traverse in Paper No. 20.

[redacted]

Response to Arguments

7. Applicants' arguments have been fully considered but they are moot in view of the new grounds of rejection set forth below.

New formal matters, objections, and/or rejections:

8. Claims 7 and 8 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In claims 7 and 8 the matrix is collagen. In claim 1 the matrix is "other than demineralized bone". Demineralized bone is primarily collagen. Claim 1 would appear to exclude collagen as a matrix.

New Claim Rejections - 35 USC § 112

9. Claims 1-10, 14-16, 20-23, 32, 33, 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a device comprising an alkyl cellulose, does not reasonably provide enablement for a device comprising a "binding agent". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The limitation "binding agent" is analogous to a single means claim of the type disparaged by the court. The problem with the phrase "binding agent" is that it covers every conceivable means which achieves the desired activity, specifically, "any physiologically compatible material which ... promotes bone and/or cartilage formation" (see page 41 of the specification), whereas the specification discloses at most carboxymethyl cellulose. As such, the term "binding agent" encompasses compounds that are structurally unrelated to carboxymethyl cellulose. The specification fails to teach the skilled artisan how to make such structurally unrelated compounds that have the desired activity or will perform in the manner instantly disclosed. Furthermore, the instant specification does not identify those structural features of a "physiologically compatible material" which are essential for the desired activity those which are not. In the absence of this information a practitioner would have to resort to a substantial amount of unduly extensive experimentation in the form of random analysis of all "physiologically compatible materials" before they could even begin to rationally make a "binding agent" other than carboxymethyl cellulose. The disclosure of a single species of "binding agent" is clearly insufficient support under 35 U.S.C. § 112, first paragraph, for claims which encompass any and all "binding agents".

10. Claims 2, 3 and 20-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 3 are indefinite because they recite the term "conservative amino acid sequence variants". Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "conservative amino acid sequence variants" an artisan cannot determine what additional or material functional limitations are placed upon a claim by the presence of this element.

Claims 20-23 are indefinite over the recitation of "(w/w)" because it is unclear whether this ratio is with respect to the device, the BMP, the carrier, the binding agent, or the matrix. The metes and bounds of the claim(s) are not clearly set forth.

New Claim Rejections - 35 USC § 102

11. Claims 1-5, 7, 15, 20, 22, 23 rejected under 35 U.S.C. 102(b) as being anticipated by Sato et al. (U21).

Sato et al. teach a device comprising HAP, fibrin, and BMP (Table 1, Group G, Subgroup 4). HAP is a non-synthetic, non-polymeric matrix material other than demineralized bone. Fibrin is a binding agent. BMP comprises an osteogenic protein capable of inducing repair of endochondral bone. The bone-inductive activity in bovine bone comprises BMP-7/OP-1. Absent evidence to the contrary is reasonable to expect that the bone-inductive activity in rabbit bone comprises BMP-7/OP-1, as recited in claims 2-5. The device was injected with a syringe, and presumably contained a wetting agent, as recited in claim 15 (page 255, paragraph bridging

columns 1-2). Sato et al. also teach a device comprising BMP and fibrin (Table 1, Group C, Subgroup 4), which is a device comprising an osteogenic protein, 1 part binding agent and 0 parts matrix, as recited in claims 20 and 22. Sato et al. also teach a device comprising BMP and HAP (Table 1, Group G, Subgroup 3), which is a device comprising an osteogenic protein, 0 parts binding agent and 1 part matrix, as recited in claim 23.

12. Claims 1-5, 7, 8-12, 15 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Kuberasampath et al. (AA).

Kuberasampath et al. (AA) teach an osteogenic device comprising a collagen-GAG matrix (column 2, last paragraph) further comprising collagen, as recited in claims 1, 7 and 8 (column 8, full paragraph 3), a binding agent, as recited in claim 1, which is methyl cellulose, as recited in claims 10-12 (column 3, full paragraph 1; column 9, full paragraph 2), and an OP-1 osteogenic protein, as recited in claims 1-5 (column 3, full paragraph 2). Saline is used as a wetting agent, as recited in claims 15 and 16 (column 3, full paragraph 4). The collagen can be obtained from skin, tendon or bones (column 5, full paragraph 1). The matrix comprises two different matrix materials, collagen and GAG, as recited in claim 9.

New Claim Rejections - 35 USC § 103

13. Claims 1, 32, 33, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath et al. (AA) as applied to claim 1 above.

Kuberasampath et al. do not teach the kit of claims 32, 33, 35 and 36. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to provide pre-formulated matrix-osteogenic protein in a receptacle and provide the binding agent and wetting agent in separate receptacles with a reasonable expectation of success. One of ordinary skill in the art would be motivated to do this so that the osteogenic device could be formulated to the desired consistency.

Alternatively, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to provide the matrix, osteogenic protein and binding agent in a single receptacle that had been pre-formulated for a pre-determined application with a reasonable expectation of success. One of ordinary skill in the art would be motivated to do so in order to prevent mistakes in the formulation of the device for a pre-determined application.

The invention is prima facie obvious over the prior art.

14. Claims 1, 13 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath et al. (AA) as applied to claim 1 above, and further in view of Wozney et al. (BE, cited by Applicants) and Amman et al. (BA, cited by Applicants).

Kuberasampath et al. teach the device of claim 1.

Kuberasampath et al. do not teach an osteogenic device comprising CMC.

Wozney et al. teach device comprising bone morphogenetic proteins, porous particulate polymers, and a sequestering agent that is either autologous blood or carboxymethyl cellulose (paragraph bridging pages 6-7; claims 1, 2 and 9-11).

Amman et al. (BA, cited by Applicants) teaches that methyl or carboxymethyl cellulose can be used for forming a gel (page 16, full paragraphs 1-2).

Wozney et al. and Amman et al. do not teach a device the device of claim 1.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to substitute CMC for methyl cellulose with a reasonable expectation of success because Wozney et al. and Amman et al. teach that CMC and MC are useful for such purposes as the device of Kuberasampath et al. was intended. The invention is prima facie obvious over the prior art.

15. Claims 1 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato et al. (U21) as applied to claim 1 above, and further in view of Wozney et al. (BE, cited by Applicants).

Sato et al. teach the device of claim 1.

Sato et al. do not teach said device comprising CMC.

[redacted]

Wozney et al. teach device comprising bone morphogenetic proteins, porous particulate polymers, and a sequestering agent that is either autologous blood or carboxymethyl cellulose (paragraph bridging pages 6-7; claims 1, 2 and 9-11).

Wozney et al. do not teach a device the device of claim 1.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to substitute methyl cellulose for fibrin with a reasonable expectation of success because Wozney et al. teach that CMC is useful for such purposes as the device of Sato et al. was intended. The invention is prima facie obvious over the prior art.

16. Claims 1, 13, 17-25 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato et al. (U21) and further in view of Wozney et al. (BE, cited by Applicants) as applied to claims 1 and 13 above and further in view of Doll et al. (V21), Cook et al. (CD, cited by Applicants), Nunez et al. (BD, cited by Applicants), Amman et al. (BA, cited by Applicants), Alberts et al: (W21), and Reddi et al. (X21)

Sato et al. and further in view of Wozney et al. teach the device of claim 1 comprising CMC.

Sato et al. and further in view of Wozney et al. do not teach said device comprising collagen.

Doll et al. teach that collagen is superior to HA for bone induction (Abstract).

[redacted]

Cook et al. discloses a composite of bovine bone collagen and rhOP-1 (page 303, column 2, full paragraph 1). The composite had the consistency of wet sand, which was spooned into the segmental defect site (paragraph bridging pages 303-304).

Nunez et al. teach that fibrin glue is a gel (page 6, lines 5-6). Soft tissue collapse into wound beds packed with DBM and osteogenin may significantly alter their osteoinductive properties and inhibit the emigration of osteoprogenitor cells into the wound bed (page 9, full paragraph 4; page 18, full paragraph 1; pages 63-64; page 70, line 20, through page 71, line 8). Nunez et al. also discloses the treatment of non-union bone defects (page 10, full paragraph 3). TSs such as FG can be molded into any desired shape; this cannot be done with DBM powder because DBM powder will not maintain its shape (page 21, full paragraph 2).

Amman et al. teaches that carboxymethyl cellulose can be used for forming a gel (page 16, full paragraphs 1-2).

Alberts et al. teach that collagen-GAG is a highly hydrated, gel-like "ground substance" (paragraph bridging pages 692-693). The GAG creates a swelling pressure, or turgor, in the extracellular matrix that resist compressive forces and allows the migration of cells and cell processes (page 705, full paragraphs 1-2).

Reddi et al. teach that biomaterials mimic the extracelluar matrix (Abstract).

Doll et al., Cook et al., Nunez et al., Amman et al., Alberts et al., and Reddi et al. do not teach the device of claims 1, 13, 17-25 and 31

[redacted]

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to (a) substitute collagen because it is superior to HA, and (b) use CMC because it forms a gel that one would reasonably expect to mimic the extracellular matrix and prevent soft tissue collapse into the wound bed, and because it can be molded into the desired shape or formulated for injection.

Generally, differences in concentrations will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentrations are critical. Furthermore, the prior reasonably teaches and/or suggest the optimization and/or varying of such concentrations. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

The invention is prima facie obvious over the prior art.

17. Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato et al. (U21) as applied to claim 1 above, and further in view of Ogawa et al. (U).

Sato et al. teach the device of claim 1. Sato et al. do not teach said device comprising two different osteogenic proteins.

Ogawa et al. teach that TGF-β and BMP synergize in promoting the formation of endochondral bone *in vivo* (page 14233, paragraph bridging columns 1-2). Ogawa et al. do not teach the device of claim 1 comprising two different osteogenic proteins.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to use TGF-β and BMP and the device of claim 1 with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to achieve a synergistic promotion of bone formation. The invention is prima facie obvious over the prior art.

18. Claims 1 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath et al. (AA) or Sato et al. (U21) in view of Wozney et al. and Amman et al. as applied to claims 1 and 13 above, and further in view of FMC Corporation (Y21).

Kuberasampath et al. or Sato et al. in view of Wozney et al. and Amman et al. teach the device of claims 1 and 13.

Kuberasampath et al. or Sato et al. in view of Wozney et al. and Amman et al do not teach said device comprising 2 different binding agents.

FMC Corp. teaches that the rheological properties of microcrystalline cellulose are modified by the addition of CMC or MC (page 4, full paragraph 1). FMC Corp. does not teach the device of claims 1 and 13 comprising 2 different binding agents.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to combine either CMC or MC with MCC, as taught by FMC Corp., in the device of claims 1 or 13 with a reasonable expectation of success. One of ordinary skill in the art

would be motivated to make this modification in order to vary the rheological properties of the device according to its desired use, such as injection. The invention is prima facie obvious over the prior art.

Conclusion

19. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 6:45 a.m. to 3:15 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310.

Official papers filed by fax should be directed to (703) 308-4242.

Faxed draft or informal communications should be directed to the examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

David Romeo

DAVID ROMEO
PATENT EXAMINER
August 15, 1999